Chemical properties of *N*-(amidomethyl)- and *N*-(imidomethyl)glycine derivatives

2.* Reactions at alkoxycarbonyl and carboxyl groups

S. G. Zlotin, I. V. Sharova, and O. A. Luk'yanov*

N. D. Zelinsky Institute of Organic Chemistry, Russian Academy of Sciences, 47 Leninsky prosp., 117913 Moscow, Russian Federation. Fax: 007 (095) 135 5328. E-mail: L121@cacr.ioc.ac.ru

N-(Aroylaminomethyl)glycine amides were synthesized by reactions of *N*-(aroylaminomethyl)glycine esters with ammonia. Alkaline hydrolysis of *N*-(amidomethyl)glycine, *N*-(imidomethyl)glycine, and *N*-(amidomethyl)phenylalanine esters afforded the corresponding *N*-(amidomethyl)-α-amino acids. Reactions of the last-mentioned compounds with ethyl esters of glycine, alanine, and phenylalanine in the presence of dicyclohexylcarbodiimide yielded dipeptides containing *N*-amidomethyl substituents.

Key words: *N*-(amidomethyl)glycine, *N*-(imidomethyl)glycine, ammonolysis, hydrolysis, dicyclohexylcarbodiimide, dipeptides.

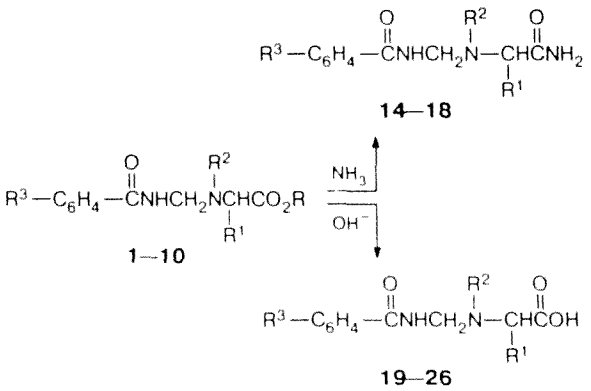
Previously, we have suggested a method for the synthesis of *N*-(amidomethyl)-[2] and *N*-(imidomethyl)glycine[3] esters based on reactions of glycine esters with formaldehyde and amides or imides. It has been demonstrated that the compounds obtained can enter into reactions of nitrosation, acylation, and sulfonylation at the amino group; these reactions proceed with retention of the $N-CH_2-N$ structural fragment and afford the corresponding *N*-nitroso, *N*-acyl, and *N*-sulfonyl derivatives.[1]

In this work, we have studied the reactions of *N*-(amidomethyl)- and *N*-(imidomethyl)-α-amino acid esters (**1**—**13**) and the products of the hydrolysis of these compounds with nucleophilic reagents with the aim of obtaining polyfunctional derivatives of glycine, including dipeptides, containing amidomethyl substituents.

It was found that *N*-(aroylaminomethyl)glycine methyl and ethyl esters containing an H atom at the amine N atom (for example, **2**) and certain of their *N*-acyl (**6** and **8**) and *N*-sulfonyl (**5** and **9**) derivatives readily react with ammonia in alcohol at 20—55 °C to produce the corresponding amides (**14**—**18**) (the yields were 41—84 %, Table 1).

In spite of the rather large distances between the substituents at the aromatic nucleus and the reaction center, the nature and positions of these substituents have a pronounced effect on the course of the reaction. Thus, *N*-(*p*-bromobenzoylaminomethyl)-*N*-acetylglycine methyl ester (**8**) readily reacts with ammonia even at ~20 °C to yield amide **17**, whereas *N*-acetyl-*N*-(*p*-nitrobenzoylaminomethyl)glycine amide (**16**) forms in a preparative yield only when the corresponding ester **6** is heated with ammonia in a sealed tube at 55 °C. Attempts to synthesize *N*-(*p*-nitrobenzoylaminomethyl)-*N*-tosylglycine amide have not met with success even under these conditions although the corresponding *m*-nitro derivative (**15**) readily forms from ester **5** at ~20 °C.

Unlike ammonia, benzylamine does not react with alkyl esters **1**—**10** under the conditions studied.



R = Et (**1**—**3**, **5**), Me (**4**, **6**—**10**);
R^1 = H (**1**—**9**, **14**—**25**), CH_2Ph (**10**, **26**);
R^2 = H (**2**, **14**), Ac (**3**, **6**, **8**, **10**, **16**, **17**, **20**, **22**, **24**, **26**), Ts (**1**, **4**, **5**, **7**, **9**, **15**, **19**, **21**, **23**, **25**);
R^3 = H (**1**, **19**), *m*-NO_2 (**2**—**5**, **14**, **15**, **20**, **21**), *p*-NO_2 (**6**, **7**, **16**, **22**, **23**, **26**), *p*-Br (**8**, **9**, **17**, **18**, **24**, **25**).

Like the reactions with ammonia, alkaline hydrolysis of esters **1**, **3**, **4**, and **6**—**10** proceeds with retention of

* For Part 1, see Ref. 1.

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Table 1. Yields, melting points, and the data of the IR and ^{1}H NMR spectra of the derivatives of *N*-(aroylaminomethyl)-α-amino acids amides (**14—18**) and *N*-(aroylaminomethyl)-α-amino acids amides (**19—29**)

Compound	Yield (%)	M.p. /°C	IR, ν/cm^{-1}			^{1}H NMR, δ (*J*/Hz)					
			C=O	NO_2	NH	NCH_2N	NCH_2C (NCHC)	R^2	Ar	CONH	Other signals
14	41	150—155	1650, 1670	1530	3320, 3345, 3445	4.18 (d, *J* = 6.0)	3.29 s	—	7.40 (m, 2 H), 7.98 (m, 2 H)	9.63 (t, *J* = 6.0)	7.55 (s, 1 H, NH_2), 8.30 (s, 1 H, NH_2)
15	64	189—192	1655, 1670	1535	3300—3340, 3380, 3460	4.98 (d, *J* = 5.6)	4.02 s	2.27 (s, 3 H, Me), 7.28 (d, 2 H, Ar), 7.70—7.82 (m, 2 H, Ar)	7.70—7.82 (m, 1 H), 8.15 (d, 1 H, *J* = 7.0), 8.39 (d, 1 H, *J* = 7.0), 8.52 (s, 1 H)	9.44 (t, *J* = 5.6)	7.19 (s, 1 H, NH_2), 7.44 (s, 1 H, NH_2)
16	84	244—246	1616, 1656, 1676	1528, 1540	3352, 3392, 3440	4.80 (d, 1.3 H, *J* = 5.4), 4.98 (d, 0.7 H, *J* = 5.4)	3.92 (s, 1.3 H), 4.10 (s, 0.7 H)	1.93 (s, 1 H, Me), 2.25 (s, 2 H, Me)	8.03 (d, 2 H, *J* = 8.0), 8.35 (d, 2 H, *J* = 8.0)	9.36 (t, 0.3 H, *J* = 5.4), 9.47 (t, 0.7 H, *J* = 5.4)	7.03 (s, 0.7 H), 7.19 (s, 0.3 H), 7.48 (s, 0.7 H), 7.52 (s, 0.3 H)
17	84	192—193.5	1630, 1650, 1685	—	3320, 3385, 3460	4.80 (d, 0.7 H, *J* = 5.7), 4.84 (d, 1.3 H, *J* = 5.7)	3.92 (s, 1.3 H), 4.09 (s, 0.7 H)	1.92 (s, 1 H, Me), 2.23 (s, 2 H, Me)	7.70 (d, 2 H, *J* = 7.7), 7.80 (d, 2 H, *J* = 7.7),	9.03 (t, 0.3 H, *J* = 5.7), 9.20 (t, 0.7 H, *J* = 5.7)	7.03 (s, 0.7 H), 7.15 (s, 0.3 H), 7.32 (s, 0.7 H), 7.50 (s, 0.3 H)
18	73	235—237	1665	—	3320, 3380, 3460	4.89 (d, *J* = 5.5)	3.93 s	2.92 (s, 3 H, Me), 7.28 (d, 2 H, Ar, *J* = 7.3), 7.60—7.71 (m, 2 H, Ar)	7.60—7.71 (m, 4 H)	9.13 (t, *J* = 5.5)	7.26 (s, 1 H), 7.43 (s, 1 H)
19	90	155—157	1665, 1720	—	3310	4.91 (d, *J* = 6.5)	4.07 s	2.30 (s, 3 H, Me), 7.28 (d, 2 H, Ar, *J* = 9.0), 7.67 (d, 2 H, Ar, *J* = 9.0)	7.38—7.55 (m, 3 H), 7.70 (d, 2 H, *J* = 9.0)	9.02 (t, *J* = 6.5)	—
20	58	154—159	1640, 1660, 1745	1540, 1560	3000, 3180, 3260	4.94 (d, *J* = 5.5)	4.08 (s, 1.4 H), 4.29 (s, 0.6 H)	1.97 (s, 0.9 H, Me), 2.30 (s, 2.1 H, Me)	7.80 (t, 1 H, *J* = 9.0), 8.30—8.47 (m, 2 H), 8.75 (s, 1 H)	9.51 (t, *J* = 5.5)	—

(to be continued)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	IR, ν/cm^{-1}			^{1}H NMR, δ (*J*/Hz)					
			C=O	NO_2	NH	NCH_2N	NCH_2C (NCHC)	R^2	Ar	CONH	Other signals
21	35	178—181	1640, 1655	1535	3100, 3190, 3240	4.90 (d, *J* = 6.3)	4.13 s	2.20 (s, 3 H, Me), 7.13 (d, 2 H, Ar, *J* = 9.0), 7.63 (d 2 H, Ar, *J* = 9.0)	7.35 (t, 1 H, *J* = 7.8), 8.11 (d, 1 H, *J* = 7.8), 7.84 (d, 1 H, *J* = 7.8), 8.58 (s, 1 H)	8.68 (t, *J* = 6.3)	—
22	85	178—179	1652, 1664, 1756	1520, 1544	3272	4.92 (d, 0.7 H, *J* = 5.8), 4.97 (d, 1.3 H, *J* = 5.8)	4.15 (s, 1.3 H), 4.27 (s, 0.7 H)	1.95 (s, 1 H, Me), 2.31 (s, 2 H, Me)	8.03 (m, 2 H), 8.23 (m, 2 H)	8.93 (t, 0.3 H, *J* = 5.8), 9.17 (t, 0.7 H, *J* = 5.8)	—
23	16	182—184	1650—1675, 1725	1535, 1545	3300	5.10 s	4.30 s	2.35 (s, 3 H, Me), 7.32 (d, 2 H, Ar, *J* = 8.6), 7.80 (d, 2 H, Ar, *J* = 8.6)	8.00 (d, 2 H, *J* = 8.6), 8.30 (d, 2 H, *J* = 8.6)	—	—
24	73	133—135	1655, 1670, 1730	—	3330	4.83 (d, *J* = 6.2)	4.03 (s, 1.3 H), 4.23 (s, 0.7 H)	1.93 (s, 1 H, Me), 2.26 (s, 2 H, Me)	7.68 (d, 2 H, *J* = 9.0), 7.78 (d, 2 H, *J* = 9.0)	9.50 (t, *J* = 6.2)	—
25	48	178—183	1660, 1710, 1725	—	3330	4.38 (d, *J* = 5.8)	4.05 s	2.30 (s, 3 H, Me), 7.29 (d, 2 H, Ar, *J* = 8.5), 7.72 (d, 2 H, Ar, *J* = 8.5)	7.60 (d, 2 H, *J* = 8.5), 7.65 (d, 2 H, *J* = 8.5)	9.10 (t, *J* = 6.2)	—
26	63	170—174	1650, 1730	1540	3300	4.33 (dd, 1 H, J_1 = 13.0, J_2 = 5.0), 4.75 (dd, 1 H, J_1 = 13.0, J_2 = 5.0)	4.40—4.48 (m, 1 H, CH)	2.26 (s, 3 H, Me)	8.00 (d, 2 H, *J* = 8.5), 8.31 (d, 2 H, *J* = 8.5)	9.20 (t, *J* = 5.0)	3.20—3.30 (m, 2 H, $\underline{CH_2}$Ar), 7.05—7.31 (m, 5 H, Ar)

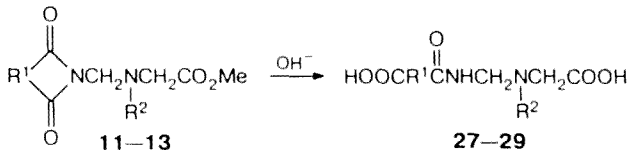
(to be continued)

Table 1 (*continued*)

Compound	Yield (%)	M.p. /°C	IR, ν/cm^{-1}			^{1}H NMR, δ (*J*/Hz)					
			C=O	NO_2	NH	NCH_2N	NCH_2C (NCHC)	R^2	Ar	CONH	Other signals
27	28	168—169	1620—1630, 1770	—	2800—3260	4.92 (d, *J* = 5.6)	4.18 (s, 1.6 H), 4.35 (s, 0.4 H)	1.97 (s, 0.6 H, Me), 2.25 (s, 2.4 H, Me)	7.40—7.59 (m, 3 H), 7.83 (d, 1 H, *J* = 7.0)	8.53 (t, 0.2 H, *J* = 5.6), 8.33 (t, 0.8 H, *J* = 5.6)	—
28	60	137—140	1600, 1660, 1715	—	3290	4.90 (d, *J* = 6.7)	4.07 s	2.42 (s, 3 H, Me), 7.38 (d, 2 H, Ar, *J* = 9.0), 7.75 (d, 2 H, Ar, *J* = 9.0)	7.08 (d, 1 H, *J* = 5.6), 7.47—7.60 (m, 2 H), 7.81 (m, 1 H)	9.00 (t, *J* = 6.7)	—
29	78	187.5—188.5	1600, 1650, 1710	—	2920—3100, 3330	4.67 (d, *J* = 7.0)	3.90 s	2.38 (s, 3 H, Me), 7.36 (d, 2 H, Ar, *J* = 9.0), 7.70 (d, 2 H, Ar, *J* = 9.0)	—	8.58 (t, *J* = 7.0)	2.21 (t, 2 H, CH_2, *J* = 6.5), 2.32 (t, 2 H, CH_2, *J* = 6.5)

the N—CH_2—N group and affords salts of the corresponding acids. The latter compounds were converted without isolation into the corresponding α-amino acids (**19—26**) by treatment with HCl (the yields were 35—90 %).

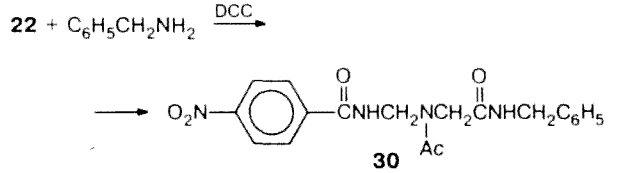
Compounds (**27—29**) containing two carboxyl groups were obtained by reactions of *N*-imidomethyl derivatives of glycine esters **11—13** with aqueous alkali followed by treatment with HCl (the yields were 28—78 %).



11—13 **27—29**

R^1 = 1,2-C_6H_4 (**11**, **12**, **27**, **28**), $(CH_2)_2$ (**13**, **29**);
R^2 = Ac (**11**, **27**), Ts (**12**, **13**, **28**, **29**).

The derivatives of *N*-(amidomethyl)-α-amino acids **19—29** are intermediates for the preparation of secondary amides (including peptides) that can not be obtained by the action of secondary amines on *N*-(amidomethyl)-α-amino acid alkyl esters. Thus, compound **22** reacts with benzylamine in the presence of dicyclohexylcarbodiimide (DCC) with retention of the N—CH_2—N group to yield amide (**30**).



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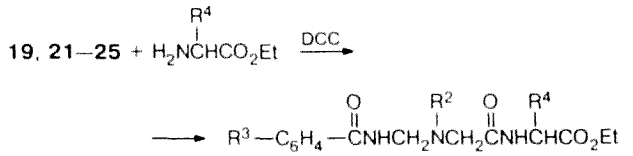
Similarly, compounds **19** and **21—25** react with ethyl esters of glycine, alanine, and phenylalanine in the presence of dicyclohexylcarbodiimide to produce *N*-(amidomethyl)dipeptides (**31—43**) (the yields were 40—80 %, Tables 2 and 3).



31—43

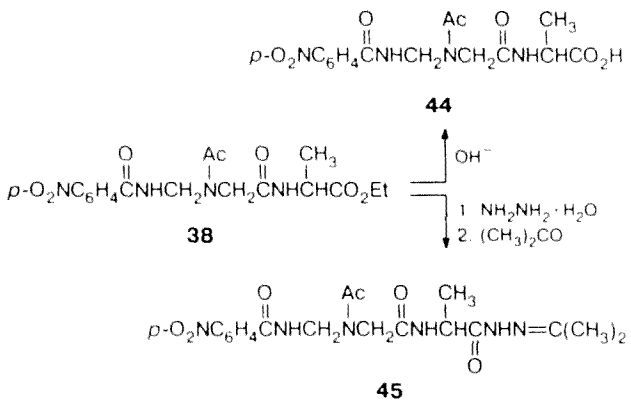
R^2 = Ac (**22**, **24**, **33**, **35**, **38**, **40**, **42**, **43**), Ts (**19**, **21**, **23**, **25**, **31**, **32**, **34**, **36**, **37**, **39**, **41**);
R^3 = H (**19**, **31**, **37**, **41**), *m*-NO_2 (**21**, **32**), *p*-NO_2 (**22**, **23**, **33**, **34**, **38**, **39**, **42**), *p*-Br (**24**, **25**, **35**, **36**, **40**, **43**);
R^4 = H (**31—36**), CH_3 (**37—40**), CH_2Ph (**41—43**).

The compounds obtained can be used to further lengthen the peptide chain, which was demonstrated by

Table 2. Yields, melting points, and the data of the IR spectra of *N*-(aroylaminomethyl)-*N*-acetylglycyl-α-amino acid ethyl esters (**33**, **35**, **38**, **40**, **42**, and **43**) and *N*-(aroylaminomethyl)-*N*-tosylglycyl-α-amino acid ethyl ester (**31**, **32**, **34**, **36**, **37**, **39**, and **41**)

Compound	Yield (%)	M.p./°C	IR, ν/cm^{-1}			
			CONH	CO_2	NH	NO_2
31	40	172—175	1640, 1685	1745	3360, 3380	—
32	25	186—188	1640, 1660	1745	3310	1540
33	47	193—195	1630—1640, 1665	1750	3340	1530, 1550
34	50	200—201	1650—1660	1750	3300	1520, 1560
35	40	158—162	1660, 1675	1750	3315	—
36	42	191—194	1660—1670	1750	3300	—
37	79	151—154	1650, 1670	1720	3310	—
38	45	173—175	1660	1740	3290	1525, 1535, 1550
39	80	129—132	1655	1740	3290	1530, 1550
40	43	138—142	1635—1660	1750	3300	—
41	74	131—133.5	1640, 1655, 1670	1735	3295	—
42	69	165—168	1630, 1660	1750	3320	1530, 1560
43	61	134—138	1630—1675	1750	3260—3340	—

reactions of hydrolysis and hydrazinolysis of ester **38**. As a result, we isolated *N*-(*p*-nitrobenzoylaminomethyl)-*N*-acetylglycylalanine (**44**) and its hydrazide, which was characterized in the form of the corresponding acetone hydrazone (**45**) (Table 3).



All the derivatives of α-amino acids and dipeptides synthesized are stable crystalline compounds. Their structures were established by IR and ^{1}H and ^{13}C NMR spectra. Purities of compounds **15**, **17**, **21**, **22**, **26—31**, **33**, **37**, **38**, **41**, and **43—45** were confirmed by the results of elemental analysis (Table 4).

Experimental

The IR spectra of solid compounds were recorded on a Specord-75-IR spectrometer using KBr pellets. The ^{1}H and ^{13}C NMR spectra were obtained on a Bruker AM-300 spectrometer in DMSO-d_6 and acetone-d_6 at frequencies of 300.13 (^{1}H) and 75.5 (^{13}C) MHz. Chemical shifts of the ^{1}H and ^{13}C signals were measured relative to DMSO-d_6 (δ, 39.5) and acetone-d_6 (δ, 30.00).

***N*-(Aroylaminomethyl)-*N*-tosyl-, *N*-(aroylaminomethyl)-*N*-acetyl-, and *N*-(*p*-nitrobenzoylaminomethyl)glycine amides (14—18).** A solution of compound **2** or compounds **5—9** (0.23 mmol) in Pr^{i}OH (3—5 mL) was saturated with ammonia at 0 °C for 10—15 min, and then the mixture was kept in a sealed tube at ~20 °C for 3—4 days (for compound **16**, at 50—55 °C for 24 h). Half the volume of the solvent was removed *in vacuo*. The precipitates of amides **14—18** were filtered off, washed with Pr^{i}OH, dried under an air stream, and recrystallized from Pr^{i}OH. The yields, melting points, and spectral characteristics of compounds **14—18** are given in Table 1.

***N*-(Aroylaminomethyl)-*N*-tosyl- and *N*-(aroylaminomethyl)-*N*-acetyl-α-amino acids (19—26).** A 45% NaOH solution (0.74 mmol, 0.45 mL) was added dropwise to a suspension of compound **1**, **3**, **4**, or **6—10** (0.68 mmol) in water (5 mL), and the mixture was stirred at 60—70 °C for 1—4 h and then at ~20 °C for 24 h. Concentrated HCl (0.74 mmol, 0.063 mL) was added to the solution, and the reaction mass was kept at +5 °C for 12 h. The precipitate of amino acid was filtered off, washed with water, and dried under an air stream (in the case of compound **20**, water was removed *in vacuo*, and the residue crystallized when the solution was treated with an ether—acetone mixture). The yields, melting points, and data of the IR and ^{1}H NMR spectra of compounds **19—26** are given in Table 1. ^{13}C NMR of compound **20** (DMSO-d_6), δ: 21.0 and 21.1 (Me); 49.7 and 50.7 (N$\underline{C}$H$_2$C); 53.8 and 53.9 (NCH$_2$N); 122.1 and 122.3 (Ar, CH); 126.0 and 126.5 (Ar, CH); 130.0 and 130.2 (Ar, CH); 133.9 and 135.3 ($\underline{C}$CO); 147.9 (CNO_2); 165.1; 170.3; 170.8 (C=O). ^{13}C NMR of compound **24** (DMSO-d_6) δ: 22.1 and 22.3 (Me); 47.2 and 50.5 (N$\underline{C}$H$_2$C); 51.5 and 54.8 (NCH$_2$N); 126.4 and 126.5 (CBr); 130.5 and 130.6 (Ar, CH); 132.4 and 132.5 (Ar, CH); 133.6 ($\underline{C}$CO); 167.4 and 167.7 (C(O)NH); 171.5; 171.8; 172.2 (CO_2).

***N*-(*o*-Carboxybenzamidomethyl)glycines (27 and 28) and *N*-(hydroxysuccinylaminomethyl)-*N*-tosylglycine (29).** A 45% NaOH solution (0.41 mmol, 0.023 mL) was added dropwise to a suspension of compounds **11—13** (0.37 mmol) in water (5 mL), and the mixture was stirred at 50—60 °C for 15—60 min. Then concentrated HCl (0.41 mmol, 0.035 mL) was added to the solution, and the reaction mixture was kept at +5 °C for 12 h. The precipitate that formed was filtered off, washed with water, and dried under an air stream. The yields, melting points, and spectral characteristics of compounds **27—29** are given in Table 1. ^{13}C NMR of compound **29** (DMSO-d_6), δ: 21.0 (Me); 28.7 and 29.7 ($(\underline{C}H_2)_2$); 47.1 (N$\underline{C}$H$_2$C); 51.8 (NCH$_2$N); 126.9 (Ar, CH); 129.6 (Ar, CH); 137.3 ($\underline{C}$Me); 143.1 (CS); 170.1; 172.6; 173.8 (CO_2).

[*N*-(*p*-Nitrobenzoylaminomethyl)-*N*-acetyl]glycine benzylamide (30). A mixture of *N*-(*p*-nitrobenzoylaminomethyl)-*N*-acetylglycine **22** (0.27 g, 0.91 mmol), benzylamine (0.096 mL, 0.84 mmol), dicyclohexylcarbodiimide (0.20 g, 0.97 mmol), and anhydrous THF (3—5 mL) was stirred at ~20 °C for 12 h. The solvent was removed *in vacuo*. Dimethylformamide (3—5 mL) was added to the residue, and the undissolved dicyclohexyl urea was filtered off. The filtrate was diluted with water (20—25 mL) and kept at +5 °C for 12 h. The precipitate that formed was filtered off, washed with water, and dried

Table 3. The data of the ^{1}H NMR spectra of *N*-(aroylaminomethyl)-*N*-acetylglycyl-α-amino acid ethyl esters (**33**, **35**, **38**, **40**, **42**, and **43**) and *N*-(aroylaminomethyl)-*N*-tosylglycyl-α-amino acid ethyl esters (**31**, **32**, **34**, **36**, **37**, **39**, and **41**)

Compound	^{1}H NMR, δ (*J*/Hz)								
	R^2	NCH_2N	NCH_2C	NCHCO	R^4	Et	NHCOAr	NHCOAlk	C_6H_4
31	2.30 (s, 3 H, Me), 7.27 (d, 2 H, Ar, *J* = 8.5), 7.73 (d, 2 H, Ar, *J* = 8.5)	4.90 (d, *J* = 5.5)	4.07 s	3.88 (d, 2 H, *J* = 6.0)	—	1.31 (t, 3 H, Me), 4.10 (q, 2 H, OCH_2)	8.98 (t, *J* = 5.5)	8.75 (t, *J* = 6.0)	7.42 (t, 2 H, *J* = 7.3), 7.52 (t, 1 H, *J* = 7.3), 7.65 (d, 2 H, *J* = 7.3)
32	2.26 (s, 3 H, Me), 7.26 (d, 2 H, Ar, *J* = 9.0), 7.72 (d, 2 H, Ar, *J* = 9.0)	4.95 (d, *J* = 5.5)	4.12 s	3.87 (d, 2 H, *J* = 6.0)	—	1.21 (t, 3 H, Me), 4.10 (q, 2 H, OCH_2)	9.40 (t, *J* = 5.5)	8.50 (t, *J* = 6.0)	7.76 (t, 1 H, *J* = 7.5), 8.10 (d, 1 H, *J* = 7.5), 8.39 (d, 1 H, *J* = 7.5), 8.48 (s, 1 H)
33	1.94 (s, 0.9 H, Me), 2.28 (s, 2.1 H, Me)	4.90 (d, 1.4 H, *J* = 5.0), 4.86 (d, 0.6 H, *J* = 5.0)	4.03 (s, 1.4 H), 4.20 (s, 0.6 H)	3.81 (d, 1.4 H, *J* = 6.5), 3.85 (d, 0.6 H, *J* = 6.5)	—	1.20 (t, 3 H, Me), 4.07 (q, 2 H, OCH_2)	9.33 (t, 0.3 H, *J* = 5.0), 9.44 (t, 0.7 H, *J* = 5.0)	8.35 (t, 0.7 H, *J* = 6.5), 8.52 (t, 0.3 H, *J* = 6.5)	8.08 (d, 2 H, *J* = 7.5), 8.35 (d, 2 H, *J* = 7.5)
34	2.28 (s, 3 H, Me), 7.27 (d, 2 H, Ar, *J* = 9.0), 7.70 (d, 2 H, Ar, *J* = 9.0)	4.95 (d, *J* = 6.0)	4.22 s	3.88 (d, 2 H, *J* = 7.0)	—	1.20 (t, 3 H, Me), 4.10 (q, 2 H, OCH_2)	9.38 (t, *J* = 6.0)	8.50 (t, *J* = 7.0)	7.80 (d, 2 H, *J* = 9.0), 8.30 (d, 2 H, *J* = 9.0)
35	1.95 (s, 0.9 H, Me), 2.25 (s, 2.1 H, Me)	4.85 (d, 0.6 H, *J* = 5.0), 4.90 (d, 1.4 H, *J* = 5.0)	4.03 (s, 1.4 H), 4.17 (s, 0.6 H)	3.83 (d, 1.4 H, *J* = 5.2), 3.87 (d, 0.6 H, *J* = 5.2)	—	1.17 (t, 3 H, Me), 4.08 (q, 2 H, OCH_2)	9.07 (t, 0.3 H, *J* = 5.0), 9.20 (t, 0.7 H, *J* = 5.0)	8.30 (t, 0.7 H, *J* = 5.2), 8.50 (t, 0.3 H, *J* = 5.2)	7.17 (d, 2 H, *J* = 7.5), 7.80 (d, 2 H, *J* = 7.5)
36	2.39 (s, 3 H, Me), 7.29 (d, 2 H, Ar, *J* = 9.6), 7.72 (d, 2 H, Ar, *J* = 9.6)	4.98 (d, *J* = 6.5)	4.07 s	3.85 (d, 2 H, *J* = 6.9)	—	1.21 (t, 3 H, Me), 4.08 (q, 2 H, OCH_2)	9.05 (t, *J* = 6.5)	8.45 (t, *J* = 6.9)	7.58 (d, 2 H, *J* = 9.5), 7.67 (d, 2 H, *J* = 9.5)
37	2.30 (s, 3 H, Me), 7.28 (d, 2 H, Ar, *J* = 7.1) 7.85 (d, 2 H, Ar, 7.1)	4.92 br.s	4.09 (s, 1.4 H), 4.26 (s, 0.6 H)	4.24 q, 1 H, *J* = 7.5)	1.27 (d, 3 H, Me, *J* = 7.5)	1.18 (t, 3 H, Me), 4.12 (q, 2 H, OCH_2)	9.00 br.s	8.18 (d, 0.3 H, *J* = 7.5), 8.40 (d, 0.7 H, *J* = 7.5)	7.44—7.60 (m, 3 H), 7.80 (d, 2 H, *J* = 7.5)

(to be continued)

Table 3 (*continued*)

Compound	^{1}H NMR, δ (*J*/Hz)								
	R^2	NCH_2N	NCH_2C	NCHCO	R^4	Et	NHCOAr	NHCOAlk	C_6H_4
38	1.95 (s, 0.9 H, Me), 2.28 (s, 2.1 H, Me)	4.85 (d, 0.6 H, *J* = 5.0), 4.90 (d, 1.4 H, *J* = 5.0)	4.05 (s, 1.4 H), 4.20 (s, 0.6 H)	4.10—4.33 (m, 1 H)	1.38 (d, 3 H, Me, *J* = 8.5)	1.16 (t, 3 H, Me), 4.07 (q, 2 H, OCH_2)	9.35 (t, 0.3 H, *J* = 5.0), 9.49 (t, 0.7 H, *J* = 5.0)	8.30 (d, 0.7 H, *J* = 8.5), 8.55 (d, 0.3 H, *J* = 8.5)	8.10 (d, 2 H, *J* = 8.0), 8.35 (d, 2 H, *J* = 8.5)
39	2.29 (s, 3 H, Me), 7.29 (d, 2 H, Ar, *J* = 8.0), 7.70 (d, 2 H, Ar, *J* = 8.0)	4.90 br.s	4.08 s	4.22 (m, 1 H)	1.25 (d, 3 H, Me, *J* = 7.3)	1.18 (t, 3 H, Me), 4.08 (q, 2 H, OCH_2)	9.35 br.s	8.41 (d, *J* = 7.3)	7.90 (d, 2 H, *J* = 8.0), 8.30 (d, 2 H, *J* = 8.0)
40	1.95 (s, 0.9 H, Me), 2.26 (s, 2.1 H, Me)	4.78—4.92 m	4.00 (s, 1.4 H), 4.19 (s, 0.6 H)	4.26 (m, 1 H)	1.26 (d, 3 H, Me, *J* = 7.5)	1.18 (t, 3 H, Me), 4.08 (q, 2 H, OCH_2)	9.10 (t, 0.3 H, *J* = 4.8), 9.21 (t, 0.7 H, *J* = 4.8)	8.29 (d, 0.7 H, *J* = 7.5), 8.50 (d, 0.3 H, *J* = 7.5)	7.71 (d, 2 H, *J* = 9.0), 7.81 (d, 2 H, *J* = 9.0)
41	2.29 (s, 2 H, Me), 2.31 (s, 1 H, Me), 7.22 (d, 2 H, Ar, *J* = 7.0), 7.70 (d, 2 H, Ar, *J* = 7.0)	4.85 (d, 1.4 H, *J* = 5.0), 4.90 (d, 0.6 H, *J* = 5.0)	4.06 (s, 1.4 H), 4.20 (s, 0.6 H)	4.47 (q, 1 H, *J* = 7.2)	2.90—3.05 (m, 2 H, CH_2), 7.18—7.35 (m, 5 H, Ar)	1.10 (t, 3 H), 4.04 (q, 2 H, OCH_2)	8.95 (t, 0.7 H, *J* = 5.0), 9.00 (t, 0.3 H, *J* = 5.0)	8.20 (d, 0.3 H, *J* = 7.5), 8.47 (d, 0.7 H, *J* = 7.5)	7.40—7.58 (m, 3 H), 7.75 (d, 2 H)
42	1.80 (s, 0.9 H, Me), 2.25 (s, 2.1 H, Me)	4.80 (d, 0.6 H, *J* = 5.0), 4.85 (d, 1.4 H, *J* = 5.0)	4.02 (s, 1.4 H), 4.12 (s, 0.6 H)	4.38—4.58 (m, 1 H)	2.80—3.08 (m, 2 H, CH_2), 7.16—7.33 (m, 5 H, Ar)	1.10 (t, 2 H, Me), 1.14 (t, 1 H, Me), 4.00 (q, 2 H, OCH_2)	9.30 (t, 0.3 H, *J* = 5.0), 9.41 (t, 0.7 H, *J* = 5.0)	8.30 (d, 0.3 H, *J* = 8.3), 8.58 (d, 0.7 H, *J* = 8.3)	8.08 (d, 2 H, *J* = 8.5), 8.34 (d, 2 H, *J* = 8.5)
43	1.78 (s, 0.9 H, Me), 2.22 (s, 2.1 H, Me)	4.70 (d, 0.6 H, *J* = 4.8), 4.84 (d, 1.4 H, *J* = 4.8)	3.90—4.15 (m, 2 H)	4.35—4.52 (m, 1 H)	2.85—3.00 (m, 2 H, CH_2), 7.15—7.32 (m, 5 H, Ar)	1.08 (t, 3 H, Me), 3.90—4.15 (m, 2 H, OCH_2)	9.05 (t, 0.3 H, *J* = 4.8), 9.20 (t, 0.7 H, *J* = 4.8)	8.32 (d, 0.7 H, *J* = 7.5), 8.55 (d, 0.3 H, *J* = 7.5)	7.70 (d, 2 H, *J* = 9.0), 7.83 (d, 2 H, *J* = 9.0)

under an air stream. Compound **30** was obtained in a yield of 0.15 g (43 %), m.p. 174—178 °C. ^{1}H NMR (DMSO-d_6), δ, *J*/Hz: 1.91 (s, 5 H, MeCO); 2.19 (s, 5 H, MeCO); 3.90 (s, 2 H, NCH_2C); 4.00 (s, 2 H, $NH\underline{CH_2}Ph$); 4.90 (br.s, 1 H, NCH_2N); 4.95 (br.s 1 H, NCH_2N); 7.28—7.40 (m, 3 H, Ar); 7.45 (br.s, 2 H, Ar); 8.10—8.12 (m, 2 H, Ar); 8.20—8.35 (m, 2 H, Ar); 9.95 (br.s, 0.5 H, NH); 10.25 (br.s, 0.5 H, NH). IR (ν/cm^{-1}): 1520; 1555 (NO_2); 1605; 1650; 1670 (C=O); 3340 (NH).

***N*-(Aroylaminomethyl)glycyl-α-amino acids ethyl esters (31—43).** A mixture of *N*-(amidomethyl)glycine **19** or **21—25** (0.68 mmol), α-amino acid ethyl ester (0.64 mmol), dicyclohexylcarboxydiimide (0.146 g, 0.71 mmol) and anhydrous THF (3—5 mL) was stirred at ~20 °C for 12 h. The solvent was removed *in vacuo*. The residue was treated with DMF (3—5 mL), and the precipitate of dicyclohexyl urea was filtered off. Ether (in the case of compounds **31—36**) or water (in the case of compounds **37—43**) (20—30 mL) was added to the filtrate, and the mixture was kept at +5 °C for 12 h. The precipitate of compounds **31—43** was filtered off, washed with ether (water), dried under an air stream, and purified by reprecipitation with ether from a methanol solution. The yields, melting points, and data of the IR and ^{1}H NMR spectra are given in Table 2. ^{13}C NMR of compound **31**

Table 4. Results of elemental analysis of the compounds synthesized

Compound	Molecular formula	Found / Calculated (%)		
		C	H	N
15	$C_{17}H_{18}N_4O_6S$	49.92 50.24	4.60 4.46	14.03 13.79
17	$C_{12}H_{14}N_3O_3Br$	44.30 43.92	4.44 4.30	13.09 12.80
21	$C_{17}H_{17}N_3O_7S$	50.43 50.12	4.28 4.21	10.15 10.31
22	$C_{12}H_{13}N_3O_6$	49.10 48.82	4.52 4.44	14.39 14.23
26	$C_{19}H_{19}N_3O_6$	59.49 59.22	5.11 4.97	11.09 10.90
27	$C_{13}H_{14}N_2O_6$	52.85 53.06	4.86 4.80	9.42 9.52
28	$C_{18}H_{18}N_2O_7S$	52.97 53.20	4.30 4.46	7.12 6.89
29	$C_{14}H_{18}N_2O_7S$	47.00 46.92	5.01 5.06	8.03 7.82
30	$C_{19}H_{20}N_4O_5$	59.69 59.37	5.32 5.24	14.36 14.58
31	$C_{21}H_{25}N_3O_6S$	56.61 56.36	5.78 5.63	9.15 9.39
33	$C_{16}H_{20}N_4O_7$	50.32 50.53	5.13 5.30	14.91 14.73
37	$C_{22}H_{27}N_3O_6S$	57.22 57.25	5.98 5.90	8.94 9.10
38	$C_{17}H_{22}N_4O_7$	52.05 51.77	5.77 5.62	13.96 14.21
41	$C_{28}H_{31}N_3O_6S$	62.37 62.55	6.00 5.81	7.91 7.82
43	$C_{23}H_{26}N_3O_5Br$	55.06 54.77	5.34 5.20	8.08 8.33
44	$C_{15}H_{18}N_4O_7$	49.59 49.18	5.21 4.95	14.97 15.29
45	$C_{18}H_{24}N_6O_6$	51.60 51.42	5.68 5.75	20.17 19.99

(DMSO-d_6), δ: 14.0 (Me); 20.9 (Me); 49.4 (N<u>C</u>H_2C); 53.6 (NCH_2N); 60.5 (OCH_2); 126.9; 127.0; 128.2; 129.5; 131.6; 133.4 (Ar, CH); 137.0 (CS); 143.1 (<u>C</u>CO); 166.9; 168.6; 169- (C=O). ^{13}C NMR of compound **33** (DMSO-d_6), δ: 14.1 (Me); 21.3 and 21.4 (Me); 40.6 and 40.8 (NH<u>C</u>H_2C); 47.1 and 50.7 (N<u>C</u>H_2C); 51.2 and 54.2 (NCH_2N); 60.5 and 60.6 (OCH_2); 123.5 and 123.6 (Ar, CH); 129.9 (Ar, CH); 139.4 and 139.5 (<u>C</u>CO); 149.2 and 149.3 (CNO_2); 165.4; 165.7; 169.2; 169.3; 169.7; 170.6; 171.4 (C=O). ^{13}C NMR of compound **35** (DMSO-d_6), δ: 14.1 (Me); 21.2 and 21.4 (Me); 46.8 (N<u>C</u>H_2C); 54.0 (NCH_2N); 60.4 (OCH_2); 125.5 (Ar, CH); 129.5 and 129.6 (Ar, CH); 131.3 and 131.4 (Ar, CH); 166.0; 169.1; 169.7; 170.4 (C=O). ^{13}C NMR of compound **36** (DMSO-d_6), δ: 14.1 (Me); 21.0 (Me); 49.7 (N<u>C</u>H_2C); 53.8 (NCH_2N); 60.7 (OCH_3); 125.6; 127.0; 129.5; 129.6; 131.4; 132.6 (Ar, CH); 137.1 (CS); 143.3 (<u>C</u>CO); 166.2; 168.7; 169.7 (C=O). ^{13}C NMR of compound **38** (DMSO-d_6), δ: 13.9 (Me); 16.8 and 17.0 (Me); 21.2 and 21.4 (MeCO); 46.7 and 47.6 (NH<u>C</u>H_2C); 47.8 and 50.5 (N<u>C</u>H_2C); 51.3 and 54.2 (NCH_2N); 60.4 (OCH_2); 123.4 and 123.6 (Ar, CH); 128.9 (Ar, CH); 139.3 (<u>C</u>CO); 149.1 and 149.2 (CNO_2); 165.3; 165.5; 166.6; 170.3; 171.2; 172.3; 172.4 (C=O).

***N*-(*p*-Nitrobenzoylaminomethyl)-*N*-acetylglycylalanine (44).** A 45% NaOH solution (0.03 mL, 0.5 mmol) was added dropwise to a suspension of compound **38** (0.17 g, 0.43 mmol) in water (3 mL), and the mixture was stirred at 60 °C for 4 h. The reaction mixture was kept at ~20 °C for 12 h and acidified with concentrated HCl (0.042 mL, 0.5 mmol). The precipitate that formed was filtered off, washed with water, and dried under an air stream. Compound **44** was obtained in a yield of 0.08 g (50 %), m.p. 126–131 °C. ^{1}H NMR (DMSO-d_6), δ, *J*/Hz: 1.29 (d, 3 H, MeCH, *J* = 8.3); 1.92 (s, 1 H, MeCO); 2.26 (s, 2 H, MeCO); 4.03 (s, 1.3 H, NCH_2C); 4.17 (s, 0.7 H, NCH_2C); 4.17–4.29 (m, 1 H, NCHC); 4.90 (d.d, 2 H, NCH_2N, *J* = 5.80); 8.10 (d.d, 2 H, Ar, *J* = 8.30); 8.20 (d, 0.7 H, NHCOAlk, *J* = 7.50); 8.32 (d.d, 2 H, Ar, *J* = 8.30); 8.40 (d, 0.3 H, NHCOAlk, *J* = 7.50); 9.30 (t, 0.3 H, NHCOAr, *J* = 4.58); 9.50 (t, 0.7 H, NHCOAr, *J* = 4.58).

***N*'-(*p*-Nitrobenzamidomethyl)-*N*'-acetylglycylalanine *N*-(isopropylidene)hydrazide (45).** Ester **38** (0.17 g, 0.43 mmol) was solved in a minimum amount of anhydrous methanol (2–3 mL) with heating, and then hydrazine hydrate (0.04 mL, 0.86 mmol) was added to the mixture. The reaction mixture was boiled for 2 h and kept at ~20 °C for 24 h. The solvent was removed *in vacuo*. The residue was treated with acetone. The precipitate was filtered off, washed with ether, and dried under an air stream. Compound **45** was obtained in a yield of 0.07 g (37 %), m.p. 189–191.5 °C. ^{1}H NMR (DMSO-d_6), δ, *J*/Hz: 1.11–1.32 (m, 3 H, MeAla); 1.85 (s, 3 H, Me); 1.91 (s, 3 H, Me); 2.10 (s, 1 H, MeCO); 2.30 (s, 2 H, MeCO); 4.05 (s, 1.3 H, NCH_2C); 4.20 (s, 0.7 H, NCH_2C); 4.38–4.53 (m, 1 H, CH); 4.78–5.00 (m, 2 H, NCH_2N); 7.98–8.18 (m, 2 H, Ar); 8.18–8.26 (m, 0.7 H, NHCOAlk); 8.26–8.41 (m, 2 H, Ar); 8.50–8.60 (m, 0.3 H, NHCOAlk); 9.32 (br.s, 0.3 H, NHCOAr); 9.49 (br.s, 0.7 H, NHCOAr); 10.02 (s, 0.3 H, NH); 10.11 (s, 0.7 H, NH). IR (ν/cm^{-1}): 1535; 1545 (NO_2); 1605; 1640–1680 (C=O); 3300 (NH).

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